PCT WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 7 :
C07D 277/34, 417/06, A61K 31/425, C07D 277/36, 277/40

A1

(11) International Publication Number: **WO 00/18746**

(43) International Publication Date: 6 April 2000 (06.04.00)

(21) International Application Number: PCT/EP99/07252

(22) International Filing Date: 30 September 1999 (30.09.99)

(30) Priority Data:
98118539.0 30 September 1998 (30.09.98) EP

(71) Applicant *(for all designated States except US)*: ROCHE DIAGNOSTICS GMBH [DE/DE]; D–68298 Mannheim (DE).

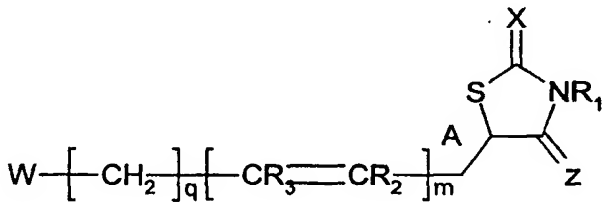
(72) Inventors; and
(75) Inventors/Applicants *(for US only)*: ESSWEIN, Angelika [DE/DE]; Birkenweg 4, D–64572 Büttelborn (DE). SCHAEFER, Wolfgang [DE/DE]; Tannhaeuserring 190, D–68199 Mannheim (DE). TSAKLAKIDIS, Christos [GR/DE]; Huegelstrasse 1/1, D–69469 Weinheim (DE). HONOLD, Konrad [DE/DE]; Suedstrasse 24, D–82377 Penzberg (DE). KALUZA, Klaus [DE/DE]; Hochfeldanger 3, D–83670 Bad Heilbrunn (DE).

(74) Common Representative: ROCHE DIAGNOSTICS GMBH; Patent Dept., D–68298 Mannheim (DE).

(81) Designated States: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published
With international search report.
Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.

(54) Title: THIAZOLIDINE DERIVATIVES FOR THE TREATMENT AND PREVENTION OF METABOLIC BONE DISORDERS



(I)

(57) Abstract

The object of the present invention are compounds of general formula (I), in which: m signifies a number between 0–8; q signifies a number between 0–8; A signifies a single or double bond; R_1 signifies hydrogen or, when X and Z are oxygen, also $-(CH_2)-COR_4$ with a =0–6; R_2, R_3 signify hydrogen or lower alkyl, whereby R_2 and R_3 can be the same or different and, when m signifies 2–8, R_2 and R_3 in the group $CR_2=CR_3$ can have various significances within the following sequence; R_4 signifies hydroxyl, lower alkoxy or the NR_1R_2 residue, whereby R_1 and R_2 can be the same or different; X signifies oxygen or imino; Z signifies oxygen, sulfur or imino; W signifies an optionally mono– or polysubstituted saturated or unsaturated mono–, bi– or tricycle which can contain one or more hetero atoms, as well as their physiologically compatible salts, esters, optically active forms, racemates, tautomers, as well as derivatives which can be metabolized *in vivo* to compounds of general formula (I), as well as the use of these compounds for the production of medicaments for the prophylaxis or therapy of metabolic bone disorders.

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AL	Albania	**ES**	Spain	**LS**	Lesotho	**SI**	Slovenia
AM	Armenia	**FI**	Finland	**LT**	Lithuania	**SK**	Slovakia
AT	Austria	**FR**	France	**LU**	Luxembourg	**SN**	Senegal
AU	Australia	**GA**	Gabon	**LV**	Latvia	**SZ**	Swaziland
AZ	Azerbaijan	**GB**	United Kingdom	**MC**	Monaco	**TD**	Chad
BA	Bosnia and Herzegovina	**GE**	Georgia	**MD**	Republic of Moldova	**TG**	Togo
BB	Barbados	**GH**	Ghana	**MG**	Madagascar	**TJ**	Tajikistan
BE	Belgium	**GN**	Guinea	**MK**	The former Yugoslav Republic of Macedonia	**TM**	Turkmenistan
BF	Burkina Faso	**GR**	Greece			**TR**	Turkey
BG	Bulgaria	**HU**	Hungary	**ML**	Mali	**TT**	Trinidad and Tobago
BJ	Benin	**IE**	Ireland	**MN**	Mongolia	**UA**	Ukraine
BR	Brazil	**IL**	Israel	**MR**	Mauritania	**UG**	Uganda
BY	Belarus	**IS**	Iceland	**MW**	Malawi	**US**	United States of America
CA	Canada	**IT**	Italy	**MX**	Mexico	**UZ**	Uzbekistan
CF	Central African Republic	**JP**	Japan	**NE**	Niger	**VN**	Viet Nam
CG	Congo	**KE**	Kenya	**NL**	Netherlands	**YU**	Yugoslavia
CH	Switzerland	**KG**	Kyrgyzstan	**NO**	Norway	**ZW**	Zimbabwe
CI	Côte d'Ivoire	**KP**	Democratic People's Republic of Korea	**NZ**	New Zealand		
CM	Cameroon			**PL**	Poland		
CN	China	**KR**	Republic of Korea	**PT**	Portugal		
CU	Cuba	**KZ**	Kazakstan	**RO**	Romania		
CZ	Czech Republic	**LC**	Saint Lucia	**RU**	Russian Federation		
DE	Germany	**LI**	Liechtenstein	**SD**	Sudan		
DK	Denmark	**LK**	Sri Lanka	**SE**	Sweden		
EE	Estonia	**LR**	Liberia	**SG**	Singapore		

Thiazolidine derivatives for the treatment and prevention of metabolic bone disorders

The present invention is concerned with thiazolidine derivatives for the treatment and prevention of metabolic bone disorders, a process for their manufacture as well as medicaments which contain these compounds.

In healthy persons the synthesis and degradation processes in bones is almost in equilibrium, i.e. the activity of the osteoblasts and osteoclasts is balanced. However, if this equilibrium is disturbed in favour of the osteoclasts and/or to the detriment of the osteoblasts, this leads to a reduction in the bone mass and to a negative change in the bone structure and function.

Hitherto, bone resorption inhibitors such as oestrogens, calcitonin and biphosphonates have primarily been used for the treatment of metabolic bone disorders. The use of these substances is, however, limited and also does not show the desired effect in all cases. Compounds which have a stimulating activity on bone synthesis and in addition contribute to an increase in an already reduced bone mass are accordingly of especial significance for the treatment of metabolic bone disorders.

Compounds having the thiazolidine structural element are known as antidiabetics, cytostatics inflammation inhibitors and for the treatment of cardiovascular illnesses and bacterial infections, with the treatment of osteoporosis in addition to an antidiabetic activity also being described in Applications EP 783888, EP 590793, EP 676398 and EP 708098.

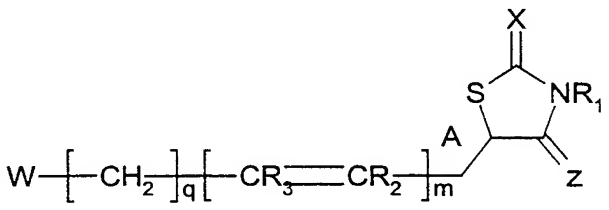
The parathyroid hormone (PTH), a hormone from the parathyroid gland, is the natural ligand of the receptor and an important regulator for the maintenance of the calcium level in the body. PTH can stimulate bone formation or bone resorption. In this, it acts as a regulatory hormone on a series of enzymes, inter alia, on adenylate cyclase (cAMP synthesis) and on ornithine decarboxylase. PTH mobilizes calcium from bones in the case of calcium deficiency, reduces calcium excretion from the kidneys and

simultaneously improves the resorption of calcium from the intestine by an increased synthesis of 1,25-$(OH)_2D_3$. A normalization of the calcium level is achieved by the action on these target organs. On the other hand, the incorporation of calcium in bones is stimulated in the case of an elevated calcium level. This osteoanabolic activity of PTH and its fragments has been attributed to the activation of adenylate cyclase and of cAMP-dependent protein kinases (Rixon, R. Whitfield, J. et al JMBR 9 (8) 1179-89 (1994).

Surprisingly, it has now been found that thiazolidine of the present invention stimulate the PTH receptor-mediated cAMP formation. Compounds of the present invention are accordingly suitable for the broad treatment of metabolic bone disorders. They can be used primarily to good effect where the bone synthesis is disturbed, i.e. they are especially suitable for the treatment of osteopenic disorders of the skeletal system such as e.g. osteoporosis, inter alia, osteogenesis imperfecta as well as for the local assistance in bone regeneration and osteoinduction such as e.g. in orthopedic and maxillary medical indications, in fracture healing, osteosyntheses, pseudoarthroses and for the healing in of bone implants. However, having regard to these properties they also find use in the prophylaxis of osteoporosis.

By their influence on bone metabolism medicaments with the thiazolidine of the present invention as active substances furthermore form a basis for the local and systemic treatment of rheumatoid arthritis, osteoarthritis and degenerative arthrosis.

The object of the present invention are compounds of general formula (I),



(I)

in which

m signifies a number between 0-8,

q signifies a number between 0-8

A	signifies a single or double bond
R_1	signifies hydrogen or, when X and Z are oxygen, also -CH_2)-COR_4 with a = 0-6
R_2,R_3	signify hydrogen or lower alkyl, whereby R_2 and R_3 can be the same or different and, when m signifies 2-8, R2 and R3 in the group CR_2=CR_3 can have various significances within the following sequence
R_4	signifies hydroxy, lower alkoxy or the NR_1R_2 residue, whereby R_1 and R_2 can be the same or different
X	signifies oxygen or imino
Z	signifies oxygen, sulphur or imino
W	signifies an optionally mono- or polysubstituted saturated or unsaturated mono-, bi- or tricycle which can contain one or more hetero atoms,

As a rule, lower alkyl signifies linear or branched alkyl residues with one to six carbon atoms, preferably methyl, ethyl, propyl, i-propyl, butyl, t-butyl, pentyl, hexyl, particularly methyl.

Alkoxy groups signify a combination of a C_1-C_{10}-alkyl group in accordance with the above definition with an oxygen atom, e.g. methoxy, ethoxy, propoxy, isopropoxy, butoxy and pentoxy groups.

Under monocycle there are to be understood optionally mono- or polysubstituted, saturated or unsaturated ring systems with 3-8, preferably 5-7 carbon atoms, which optionally can be interrupted by one or more hetero atoms, such as nitrogen, oxygen or sulphur, especially the phenyl, pyridyl, pyrimidinyl, pyridazinyl, pyrazinyl, cyclopentyl, cyclohexyl, cyclohexenyl, cycloheptyl, morpholinyl, thiamorpholinyl, piperidinyl, piperazinyl, tetrahydrofuranyl, tetrahydropyranyl, furyl, thiophenyl, imidazolyl thiazolyl, oxazolyl, isothiazolyl, isoxazolyl, 1,2,3-triazolyl or 1,2,4-triazolyl residue, as well as residues such as e.g. phenyl phenyl ether, diphenylmethane and biphenyl. As substituents there come into consideration primarily lower alkyl, alkylcarbonyl, alkoxy, alkoxycarbonylalkoxy, amino, benzyl, benzyloxy, carboxyl, dialkylamino, dioxymethylene, diphenylamino, hydroxy, mercaptoalkyl, phenoxy, styryl and halogen.

In the case of the bicycle set forth under W, this is preferably a residue such as the naphthyl, tetrahydronaphthyl, decalinyl, quinolinyl, chromane, chromene, isoquinolinyl, tetrahydroquinolinyl, tetrahydroisoquinolinyl, indolyl, benzimidazolyl, indazolyl,

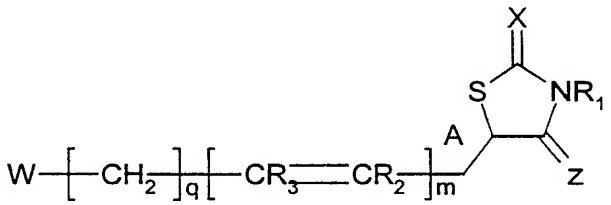
oxindolyl, benzofuranyl, benzothiophenyl, benzothiazolyl, benzoxazolyl or purinyl residue, especially the indolyl, naphthyl, benzimidazolyl, quinolinyl, tetrahydroquinolinyl benzothiophenyl and benzofuranyl residue, which optionally can be mono- or polysubstituted. As substituents there come into consideration primarily lower alkyl, alkylcarbonyl, alkoxy, alkoxycarbonylalkoxy, amino, benzyl, benzyloxy, carboxyl, dialkylamino, dioxymethylene, diphenylamino, hydroxy, mercaptoalkyl, phenoxy, styryl and halogen.

In the case of the tricycle set forth under W, this is preferably a residue such as the anthracene, fluorene, dibenzofuran or carbazole residue.

Compounds of formula I wherein W is phenyl, naphthyl, indolyl, benzofuranyl or benzothiophenyl, X is oxygen, m and g are both 0 and R_1 is hyxdrogen are disclosed in EP-A-0434394 however for the treatment of inflammatory lowel diseases.

Compounds of formula I wherein W is an amino substituted phenyl or indolyl, X is imino, m and q both are 0 and R_1 is hydrogen are disclosed in USP 5.143.929, however for the treatment of inflammatory.

Therefore subject of the present invention are also new compounds of general formula I



(I)

in which

m signifies a number between 0-8,

q signifies a number between 0-8

A signifies a single or double bond

R_1 signifies hydrogen or, when X and Z are oxygen, also -CH_2)-COR_4 with a = 0-6

R_2,R_3 signify hydrogen or lower alkyl, whereby R_2 and R_3 can be the same or different and, when m signifies 2-8, R2 and R3 in the group CR_2=CR_3 can have various significances within the following sequence

R_4 signifies hydroxy, lower alkoxy or the NR_1R_2 residue, whereby R_1 and R_2 can be the same or different

X signifies oxygen or imino

Z signifies oxygen, sulphur or imino

W signifies an optionally mono- or polysubstituted saturated or unsaturated mono-, bi- or tricycle which can contain one or more hetero atoms,

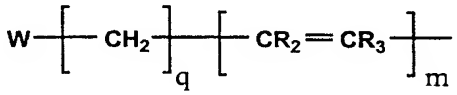
whereas W is not phenyl, naphthyl, indolyl, benzofuranyl and benzothiphen-yl, if X signifies oxygen, m and q are both 0 and R_1 is hydrogen,

whereas W is not an aminosubstituted phenyl and indolyl, if X signifies imino, m and q both are 0 and R1 is hydrogen,

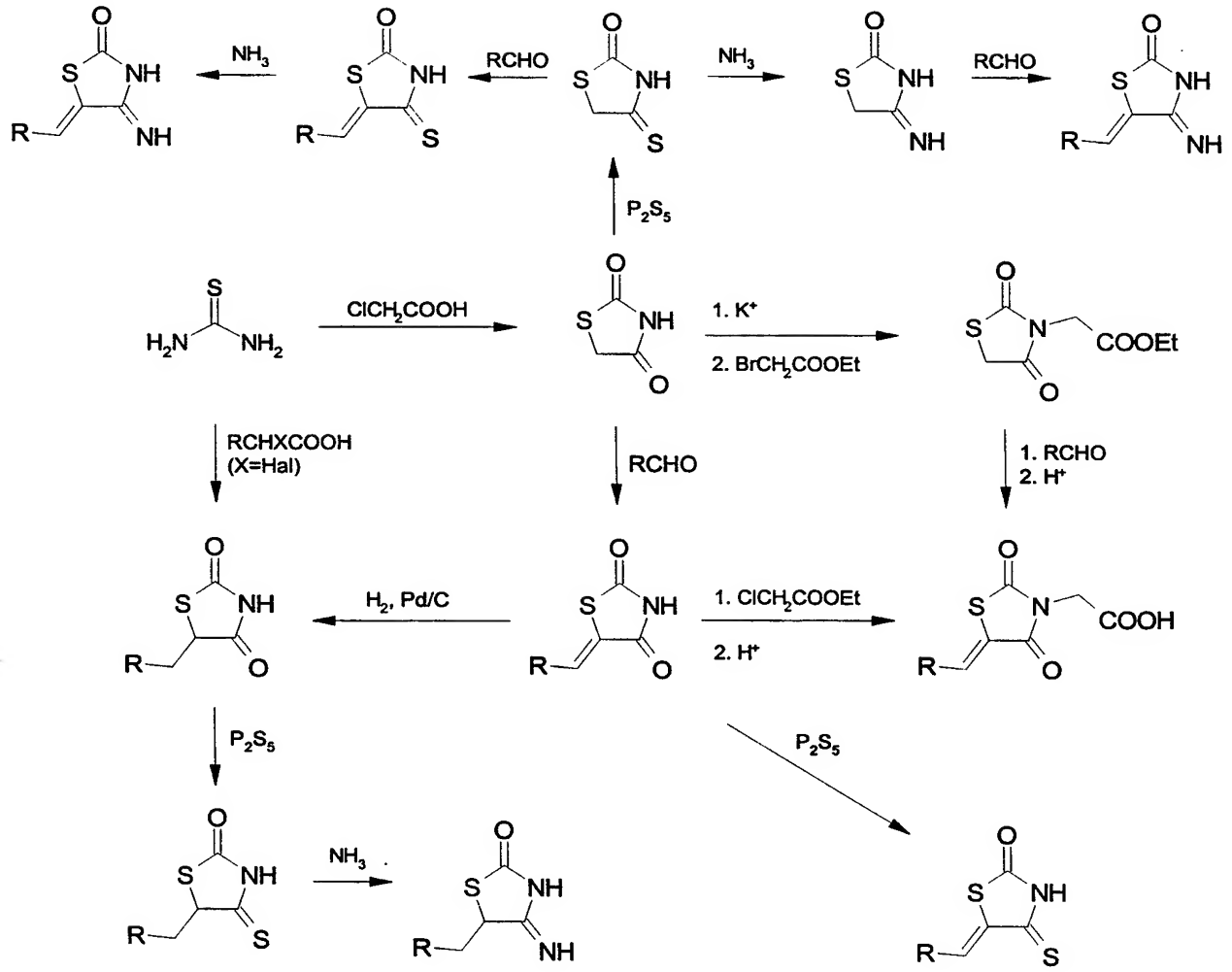
as well as their physiologically compatible salts, esters, optically active forms, racemates, tautomers, as well as derivatives which can be metabolized *in vivo* to compounds of general formula (I), as well as the use of these compounds for the production of medicaments.

Preferred are compounds of general formula (I) in which m signifies a number between 0 and 4, q signifies the number 0 or 1, A signifies a double bond, R_1 signifies hydrogen or a group $-(CH_2)_a-COR_4$, a preferably signifies a number between 1 and 3, R_4 signifies hydroxyl, methoxy or ethoxy, R_2 and, respectively, R_3 signify hydrogen or methyl, X and Z signify oxygen and W signifies an optionally mono- or polysubstituted naphthalene, phenyl, thiophene, indole, furan, benzothiophene, cyclohexenyl or biphenyl residue.

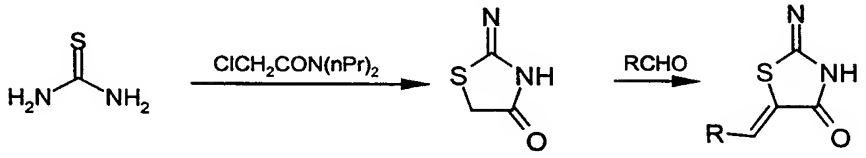
The manufacture of the compounds of general formula (I) is possible according to methods known per se. An overview of the methods of synthesis is set forth in Schemes 1 and 2; whereby R signifies the group:



Scheme 1



Scheme 2



The α-halocarboxylic acids and aldehydes used as starting materials are either commercially available, known or can be prepared analogously to the generally known processes.

Compounds of formula (I) can be administered (sic) in liquid, solid or aerosol form orally, enterally, parenterally, topically, nasally, pulmonary or rectally in all usual non-toxic pharmaceutically acceptable carrier materials, adjuvants and additives. The compounds of formula (I) can also be applied locally to/in the bones (optionally with surgical intervention). The term parenteral embraces subcutaneous, intravenous and intramuscular delivery or infusions. Oral administration forms can be e.g. tablets, capsules, dragees, syrups, solutions, suspensions, emulsions, elixirs etc., which can contain one or more additives from the following groups, such as flavourings, sweeteners, colouring agents and preservatives. Oral administration forms contain the active ingredient together with non-toxic, pharmaceutically acceptable carrier materials which are suitable for the production of tablets, capsules, dragees etc., such as e.g. calcium carbonate, sodium carbonate, lactose, calcium phosphate or sodium phosphate; starch, mannitol, methylcellulose, talc, highly dispersible silicic acids, high molecular fatty acids (such as stearic acid), groundnut oil, olive oil, paraffin, miglyol, gelatine, agar-agar, magnesium stearate, beeswax, cetyl alcohol, lecithin, glycerol, animal and vegetable fats, solid high molecular polymers (such as polyethylene glycol). Tablets, capsules, dragees etc. can be provided with an appropriate coating, e.g. glyceryl mono-stearate or glyceryl distearate, in order to prevent undesired side effects in the gastro-intestinal tract or to give a longer duration of action by the delayed absorption in the gastrointestinal tract. As the injection medium there are preferably used sterile injectable aqueous or oily solutions or suspensions which contain the usual additives such as stabilizers and solubilizers. Such additives can be e.g. water, isotonic saline, 1,3-butanediol, fatty acids (such as oleic acid), mono- and diglycerides or miglyol. For rectal use there can be used all suitable non-irritating additives which are solid at normal temperatures and liquid at rectal temperatures, such as e.g. cocoa butter and polyethylene glycol. Pharmaceutically usual carrier media are used for application as aerosols. Creams, tinctures, gels, solutions or suspensions etc. with the pharmaceutically usual additives are used for external application. The dosage can depend n a variety of factors such as mode of administration, species, age and/or individual condition. The doses to be administered daily or at intervals lie at 1-

1000 mg/individual, preferably at 10-250 mg/individual, and can be taken at one time or divided over several times.

The compounds of formula (I) can also be applied locally to/in the bones (optionally with surgical intervention). The application directly to/in the bones (optionally with surgical intervention) can be effected locally or carrier-bonded either in solution or suspension, conveniently by infusion or injection. Carrier-bonded compounds of formula (I) can be administered, for example, as gels, pastes, solids or as a coating on implants.

Biocompatible and preferably biodegradable materials are used as the carrier. Preferably, the materials themselves also induce wound healing or osteogenesis.

For local application it is preferred that the compounds of formula (I) are imbedded in polymer gels or films in order to immobilize them and to apply these preparations directly on the site of the bone to be treated. Such polymer-based gels or films consist, for example, of glycerine, methylcellulose, hyaluronic acid, polyethylene oxides and/or poloxamers. Also suitable are collagen, gelatines and alginates and are described, for example, in WO 93/00050 and WO 93/20859. Further polymers are polylactic acid (PLA) and copolymers of lactic acid and glycolic acid (PLPG) (Hollinger el al., J. Biomed. Mater. Res. 17 71-82 (1983)) as well as the bone derivative "Demineralized Bone Matrix" (DBM) (Guterman et al. Kollagen Rel. Res. 8 419-4319 (1988). Also suitable are polymers as are used, for example, for the adsorption of TGFβ and which are described in EP-A 0 616 814 and EP-A-0 567 391 and synthetic bone matrices in accordance with WO 91/18558.

Likewise suitable as carriers for the compounds of formula (I) are materials which are usually used for the implantation of bone substitutes or otherwise of therapeutically active substances. Such carriers are based, for example, on calcium sulphate, tricalcium phosphate, hydroxylapatite (sic) and its biodegradable derivatives and polyanhydrides. Apart from these biodegradable carriers there are also suitable carriers which are not biodegradable, but which are biocompatible. Such carriers are, for example, sintered hydroxylapatite, bioglass, aluminates or other ceramic materials (e.g. calcium aluminium phosphate). These materials are preferably used in combination with the biodegradable materials, such as especially polylactic acid, hydroxylapatite, collagen or

tricalcium phosphate. Further non-degradable carriers are described, for example, in US Patent 4,164,560.

It is especially preferred to use a carrier which liberates the compounds of formula (I) continuously at the target site. Especially suitable for this are e.g. "slow release pellets" from Innovative Research of America, Toledo, Ohio, USA. Pellets which release the compounds of formula (I) over several days, preferably up to 100 days with a daily dosage of 1-10 mg/kg per day, are especially preferred.

Preferred in the scope of the present invention are, apart form the compounds named in the Examples and compounds derivable by a combination of all of the significances of the substituents set forth in the claims, the following derivatives as well as their physiologically compatible salts, esters, optically active forms, racemates, tautomers as well as derivatives which can be metabolized *in vivo* to compounds of general formula (I), as well as the use of these compounds for the production of medicaments,

Preferred Compounds (PC):

1. 5-(9*H*-Fluoren-2-ylmethylene)-thiazolidin-2,4-dione
2. 5-Phenanthren-9-ylmethylene-4-thioxo-thiazolidin-2-one
3. 5-Anthracen-9-ylmethylene-4-imino-thiazolidin-2-one
4. 2-Imino-5-(10-methyl-anthracen-9-ylmethylene)-thiazolidin-4-one
5. [5-(3-Furan-2-yl-allylidene)-2,4-dioxo-thiazolidin-3-yl]-acetic acid
6. 5-Benzyl-thiazolidin-2,4-dione
7. 5-[3-(2-Methoxy-phenyl)-allylidene]-thiazolidine-2,4-dione
8. 5-(2,3-Dimethoxy-benzylidene)-thiazolidine-2,4-dione
9. 4-Thioxo-5-(2,3,4-trimethoxy-benzylidene)-thiazolidin-2-one
10. 5-(2,4-Dimethoxy-benzylidene)-4-imino-thiazolidin-2-one
11. 2-Imino-5-(2,4,5-trimethoxy-benzylidene)-thiazolidin-4-one
12. [2,4-Dioxo-5-(2,4,6-trimethoxy-benzylidene)-thiazolidin-3-yl]-acetic acid
13. 5-(2,5-Dimethoxy-benzyl)-thiazolidine-2,4-dione
14. 5-[3-(2-Ethoxy-phenyl)-allylidene]-thiazolidine-2,4-dione
15. 5-(2-Hydroxy-benzylidene)-thiazolidine-2,4-dione
16. 5-(2-Hydroxy-3-methoxy-benzylidene)-4-thioxo-thiazolidin-2-one
17. 5-(3-Ethoxy-2-hydroxy-benzylidene)-4-imino-thiazolidin-2-one

18. 5-(2,3-Dihydroxy-benzylidene)-2-imino-thiazolidin-4-one
19. [2,4-Dioxo-5-(2,3,4-trihydroxy-benzylidene)-thiazolidin-3-yl]-acetic acid
20. 5-(4-Diethylamino-2-hydroxy-benzyl)-thiazolidine-2,4-dione
21. 5-[3-(2-Hydroxy-4-methoxy-phenyl)-allylidene]-thiazolidine-2,4-dione
22. 5-(2,4,6-Trihydroxy-benzylidene)-thiazolidine-2,4-dione
23. 5-(2-Hydroxy-5-methoxy-benzylidene)-4-thioxo-thiazolidin-2-one
24. 5-(2,5-Dihydroxy-benzylidene)-4-imino-thiazolidin-2-one
25. 2-Imino-5-(2-methyl-benzylidene)-thiazolidin-4-one
26. [5-(4-Methoxy-2,3-dimethyl-benzylidene)-2,4-dioxo-thiazolidin-3-yl]-acetic acid
27. 5-(2,4,6-Trimethyl-benzyl)-thiazolidine-2,4-dione
28. 5-[3-(2,5-Dimethyl-phenyl)-allylidene]-thiazolidine-2,4-dione
29. 5-(4-Methoxy-2,5-dimethyl-benzylidene)-thiazolidine-2,4-dione
30. 5-[3-(4-Methoxy-phenoxy)-benzylidene]-4-thioxo-thiazolidin-2-one
31. 5-[3-(4-*tert*-Butyl-phenoxy)-benzylidene]-4-imino-thiazolidin-2-one
32. 2-Imino-5-(3-*p*-tolyloxy-benzylidene)-thiazolidin-4-one
33. [5-(3-Methoxy-benzylidene)-2,4-dioxo-thiazolidin-3-yl]-acetic acid
34. 5-(3,4-Dimethoxy-benzyl)-thiazolidine-2,4-dione
35. 5-[3-(3,4,5-Trimethoxy-phenyl)-allylidene]-thiazolidine-2,4-dione
36. 5-(4-Benzyloxy-3-methoxy-benzylidene)-thiazolidine-2,4-dione
37. 5-(3,5-Dimethoxy-benzylidene)-4-thioxo-thiazolidin-2-one
38. 5-(3-Benzyloxy-benzylidene)-4-imino-thiazolidin-2-one
39. 5-(3-Hydroxy-benzylidene)-2-imino-thiazolidin-4-one
40. [5-(3-Hydroxy-4-methoxy-benzylidene)-2,4-dioxo-thiazolidin-3-yl]-acetic acid
41. 5-(3,4-Dihydroxy-benzyl)-thiazolidine-2,4-dione
42. 5-(3-*m*-Tolyl-allylidene)-thiazolidine-2,4-dione
43. 5-(4-Methoxy-3-methyl-benzylidene)-thiazolidine-2,4-dione
44. 5-(4-Dimethylamino-benzylidene)-4-thioxo-thiazolidin-2-one
45. 5-(4-Diethylamino-benzylidene)-4-imino-thiazolidin-2-one
46. 2-Imino-5-(4-phenoxy-benzylidene)-thiazolidin-4-one
47. [5-(4-Methoxy-benzylidene)-2,4-dioxo-thiazolidin-3-yl]-acetic acid
48. 5-(3-Benzyloxy-4-methoxy-benzyl)-thiazolidine-2,4-dione
49. 5-[3-(4-Benzyloxy-phenyl)-allylidene]-thiazolidine-2,4-dione
50. 5-(4-Ethoxy-benzylidene)-thiazolidine-2,4-dione
51. 5-(4-Butoxy-benzylidene)-4-thioxo-thiazolidin-2-one
52. 4-Imino-5-naphthalen-1-ylmethylene-thiazolidin-2-one

53. 2-Imino-5-(2-methoxy-naphthalen-1-ylmethylene)-thiazolidin-4-one
54. [5-(2-Hydroxy-naphthalen-1-ylmethylene)-2,4-dioxo-thiazolidin-3-yl]-acetic acid
55. 5-(4-Methoxy-naphthalen-1-ylmethyl)-thiazolidine-2,4-dione
56. 5-(3-Naphthalen-2-yl-allylidene)-thiazolidine-2,4-dione
57. 5-(3,4-Bis-benzyloxy-benzylidene)-thiazolidine-2,4-dione
58. 5-(9-Ethyl-9*H*-carbazol-3-ylmethylene)-4-thioxo-thiazolidin-2-one
59. 4-Imino-5-(1*H*-indol-3-ylmethylene)-thiazolidin-2-one
60. 2-Imino-5-(5-methoxy-1*H*-indol-3-ylmethylene)-thiazolidin-4-one
61. (5-Benzo[1,3]dioxol-5-ylmethylene-2,4-dioxo-thiazolidin-3-yl)-acetic acid
62. 5-Quinolin-4-ylmethyl-thiazolidine-2,4-dione
63. 5-[3-(4-Hydroxy-phenyl)-allylidene]-thiazolidine-2,4-dione
64. 5-(4-Hydroxy-3-methoxy-benzylidene)-thiazolidine-2,4-dione
65. 5-(4-Hydroxy-3,5-dimethoxy-benzylidene)-4-thioxo-thiazolidin-2-one
66. 5-(3-Ethoxy-4-hydroxy-benzylidene)-4-imino-thiazolidin-2-one
67. 5-(4-Hydroxy-3,5-dimethyl-benzylidene)-2-imino-thiazolidin-4-one
68. (5-Biphenyl-4-ylmethylene-2,4-dioxo-thiazolidin-3-yl)-acetic acid
69. 5-(4-Methylsulphanyl-benzyl)-thiazolidine-2,4-dione
70. 5-[3-(4-Isopropyl-phenyl)-allylidene]-thiazolidine-2,4-dione
71. 5-(4-Methyl-benzylidene)-thiazolidine-2,4-dione
72. 5-(4-Ethyl-benzylidene)-4-thioxo-thiazolidin-2-one
73. 5-(2,2-Diphenyl-ethylidene)-4-imino-thiazolidin-2-one
74. [5-(2-Methyl-3-phenyl-allylidene)-2,4-dioxo-thiazolidin-3-yl]-acetic acid
75. 5-(2-Pentyl-3-phenyl-allyl)-thiazolidine-2,4-dione
76. 5-(4-Hexyl-5-phenyl-penta-2,4-dienylidene)-thiazolidine-2,4-dione
77. 5-Phenethylidene-thiazolidine-2,4-dione-2-one
78. 4-Imino-5-(3-phenyl-allylidene)-thiazolidin-2-one
79. 2-Imino-5-[3-(2-methoxy-phenyl)-allylidene]-thiazolidin-4-one
80. {5-[3-(4-Dimethylamino-phenyl)-allylidene]-2,4-dioxo-thiazolidin-3-yl}-acetic acid
81. 5-(3-Phenyl-propyl)-thiazolidine-2,4-dione
82. 5-[3-(3,5-Di-*tert*-butyl-4-hydroxy-phenyl)-allylidene]-thiazolidine-2,4-dione
83. 5-(2,3-Dihydro-benzo[1,4]dioxin-6-ylmethylene)-thiazolidine-2,4-dione
84. 5-(3-Ethoxy-4-methoxy-benzylidene)-4-thioxo-thiazolidin-2-one
85. 5-(4-Diethoxymethyl-benzylidene)-4-imino-thiazolidin-2-one

86. 5-(4-Dimethylamino-naphthalen-1-ylmethylene)-2-imino-thiazolidin-4-one
87. 5-(2,4-Dimethoxy-3-methyl-benzyl)-thiazolidine-2,4-dione
88. 5-(4-Styryl-benzylidene)-thiazolidine-2,4-dione
89. 5-[4-(3-Dimethylamino-propoxy)-benzylidene]-4-thioxo-thiazolidin-2-one
90. 5-(2,4-Dihydroxy-benzylidene)-4-imino-thiazolidin-2-one
91. 2-Imino-5-(2-methyl-1*H*-indol-3-ylmethylene)-thiazolidin-4-one
92. [5-(4-Hydroxy-3-methyl-benzylidene)-2,4-dioxo-thiazolidin-3-yl]-acetic acid
93. 5-(2-Hexyloxy-benzyl)-thiazolidine-2,4-dione
94. 5-(4-Allyloxy-benzylidene)-thiazolidine-2,4-dione
95. 5-(4-Propoxy-benzylidene)-4-thioxo-thiazolidin-2-one
96. 4-Imino-5-(4-pentyloxy-benzylidene)-thiazolidin-2-one
97. 2-Imino-5-(4-octyloxy-benzylidene)-thiazolidin-4-one
98. [5-(5-Benzyloxy-1*H*-indol-3-ylmethylene)-2,4-dioxo-thiazolidin-3-yl]-acetic acid
99. 5-Benzofuran-2-ylmethyl-thiazolidine-2,4-dione
100. 5-(4-Pyrrolidin-1-yl-benzylidene)-thiazolidine-2,4-dione
101. 5-(2,3,4,5,6-Pentamethyl-benzylidene)-4-thioxo-thiazolidin-2-one
102. 5-(2-Benzyloxy-benzylidene)-4-imino-thiazolidin-2-one
103. 2-Imino-5-(2,3,4-trimethoxy-6-methyl-benzylidene)-thiazolidin-4-one
104. [5-(3-Ethoxy-benzylidene)-2,4-dioxo-thiazolidin-3-yl]-acetic acid
105. 5-(3,4-Dihydroxy-5-methoxy-benzyl)-thiazolidine-2,4-dione
106. 5-(3,5-Dihydroxy-benzylidene)-thiazolidine-2,4-dione
107. 5-(3,4-Dimethyl-benzylidene)-4-thioxo-thiazolidin-2-one
108. 5-(4-Ethoxy-3-methoxy-benzylidene)-4-imino-thiazolidin-2-one
109. [5-(4-Heptyloxy-benzylidene)-2,4-dioxo-thiazolidin-3-yl]-acetic acid
110. 5-Benzo[1,3]dioxol-4-ylmethyl-thiazolidine-2,4-dione
111. 5-[3-(4-Methoxy-phenyl)-allylidene]-thiazolidine-2,4-dione
112. 4-Thioxo-5-(2,4,5-trimethyl-benzylidene)-thiazolidin-2-one
113. 5-(4-Decyloxy-benzylidene)-4-imino-thiazolidin-2-one
114. [5-(4-*tert*-Butyl-benzylidene)-2,4-dioxo-thiazolidin-3-yl]-acetic acid
115. (3-Allyl-2-hydroxy-benzylidene)-4-thioxo-thiazolidin-2-one
116. 5-(4-Amino-benzylidene)-4-imino-thiazolidin-2-one
117. [5-(4-Butyl-benzylidene)-2,4-dioxo-thiazolidin-3-yl]-acetic acid
118. 5-(4-*tert*-Butoxy-benzyl)-thiazolidine-2,4-dione
119. 5-(4-Propyl-benzylidene)-thiazolidine-2,4-dione
120. 5-(4-Hexyl-benzylidene)-4-thioxo-thiazolidin-2-one

121. 4-Imino-5-(4-octyl-benzylidene)-thiazolidin-2-one
122. [2,4-Dioxo-5-(4-pentyl-benzylidene)-thiazolidin-3-yl]-acetic acid
123. 5-(3-Amino-benzyl)-thiazolidine-2,4-dione
124. 5-(2-Ethoxy-naphthalen-1-ylmethylene)-thiazolidine-2,4-dione
125. 5-(7-Methyl-1*H*-indol-3-ylmethylene)-4-thioxo-thiazolidin-2-one
126. 5-[3-(4-*tert*-Butyl-phenyl)-2-methyl-propylidene]-4-imino-thiazolidin-2-one
127. [5-(3,5-Dimethyl-1-phenyl-1*H*-pyrazol-4-ylmethylene)-2,4-dioxo-thiazolidin-3-yl]-acetic acid 5-(4-Hydroxy-2-methoxy-benzylidene)-4-thioxo-thiazolidin-2-one
128. 5-(2,2-Dimethyl-chroman-6-ylmethylene)-4-imino-thiazolidin-2-one
129. 5-(4-Methyl-naphthalen-1-ylmethyl)-thiazolidine-2,4-dione
130. 5-(3-Furan-2-yl-2-methyl-allylidene)-thiazolidine-2,4-dionepropylidene-2-one; 5-(2,3-Dihydro-benzofuran-5-ylmethylene)-4-imino-thiazolidin-2-one
131. {5-[3-(4-Diethylamino-phenyl)-allylidene]-2,4-dioxo-thiazolidin-3-yl}-acetic acid
132. 5-(4-Isobutyl-benzyl)-thiazolidine-2,4-dione
133. 5-[3-(4-Hydroxy-3-methoxy-phenyl)-allylidene]-thiazolidine-2,4-dione
134. 5-(6-Methoxy-naphthalen-2-ylmethylene)-4-thioxo-thiazolidin-2-one
135. 5-(3,5-Dimethyl-benzylidene)-4-imino-thiazolidin-2-one
136. [2,4-Dioxo-5-(4-phenylethynyl-benzylidene)-thiazolidin-3-yl]-acetic acid
137. 5-[3-(4-*tert*-Butyl-phenyl)-2-methyl-allylidene]-thiazolidine-2,4-dione
138. 5-(4-Octadecyloxy-benzylidene)-4-thioxo-thiazolidin-2-one
139. 5-(4-Diphenylamino-benzylidene)-4-imino-thiazolidin-2-one
140. [5-(4-Dimethylamino-2-methoxy-benzylidene)-2,4-dioxo-thiazolidin-3-yl]-acetic acid
141. 5-(2-Benzyloxy-4,5-dimethoxy-benzyl)-thiazolidine-2,4-dione
142. 5-[3-(2-Hydroxy-ethoxy)-benzylidene]-thiazolidine-2,4-dione
143. 5-[2-(2-Hydroxy-ethoxy)-benzylidene]-4-thioxo-thiazolidin-2-one
144. 5-[4-(2-Hydroxy-ethoxy)-benzylidene]-4-imino-thiazolidin-2-one
145. [5-(4-*tert*-Butoxycarbonyloxy-3-methoxy-benzylidene)-2,4-dioxo-thiazolidin-3-yl]-acetic acid
146. 5-[3-(4-Hydroxy-3,5-dimethoxy-phenyl)-allylidene]-thiazolidine-2,4-dione
147. 5-(2-Benzyloxy-3-methoxy-benzylidene)-4-thioxo-thiazolidin-2-one
148. 4-Imino-5-(4-methanesulphonyl-benzylidene)-thiazolidin-2-one
149. (5-Benzo[*b*]thiophen-2-ylmethylene-2,4-dioxo-thiazolidin-3-yl)-acetic acid
150. 5-(3-Benzo[*b*]thiophen-2-yl-allylidene)-thiazolidine-2,4-dione
151. 5-Thiophen-2-ylmethylene-4-thioxo-thiazolidin-2-one

152. 4-Imino-5-(3-naphthalen-2-yl-allylidene)-thiazolidin-2-one
153. [5-(2-[1,3]Dioxolan-2-yl-6-fluoro-benzylidene)-2,4-dioxo-thiazolidin-3-yl]-acetic acid
154. 5-(2,4-Bis-benzyloxy-benzylidene)-thiazolidine-2,4-dione
155. 5-(4-Benzyl-benzylidene)-4-thioxo-thiazolidin-2-one
156. 5-[3,7-Dimethyl-9-(2,6,6-trimethyl-cyclohex-1-enyl)-nona-2,4,6,8-tetraenylidene]-4-imino-thiazolidin-2-one
157. (5-Furan-2-ylmethylene-2,4-dioxo-thiazolidin-3-yl)-acetic acid
158. 5-Pyridin-2-ylmethylene-thiazolidine-2,4-dione
159. 5-(1-Methyl-1*H*-pyrrol-3-ylmethylene)-4-thioxo-thiazolidin-2-one
160. 5-(2-Hydroxy-4,6-dimethoxy-benzylidene)-4-imino-thiazolidin-2-one
161. [5-(5-Benzyloxy-2-hydroxy-benzylidene)-2,4-dioxo-thiazolidin-3-yl]-acetic acid
162. 5-(4-Benzyloxy-3,5-dimethoxy-benzylidene)-thiazolidine-2,4-dione
163. 5-(4-Benzyloxy-3,5-dihydroxy-benzylidene)-4-thioxo-thiazolidin-2-one
164. 5-(2,5-Bis-benzyloxy-benzylidene)-4-imino-thiazolidin-2-one
165. (5-Cyclohexylmethylene-2,4-dioxo-thiazolidin-3-yl)-acetic acid
166. 5-(3-Biphenyl-4-yl-allylidene)-thiazolidine-2,4-dione
167. 5-(3,4-Diethoxy-2,5-dimethyl-benzylidene)-4-thioxo-thiazolidin-2-one
168. 5-[3-(3,4-Diethoxy-2,5-dimethyl-phenyl)-allylidene]-4-imino-thiazolidin-2-one
169. 2-(3-Carboxymethyl-2,4-dioxo-thiazolidin-5-ylidenemethyl)-benzoic aid
170. 5-(2,4-Dioxo-thiazolidin-5-ylidenemethyl)-2-hydroxy-benzoic aid
171. Methyl 4-(2-oxo-4-thioxo-thiazolidin-5-ylidenemethyl)-benzoate
172. 4-(4-Imino-2-oxo-thiazolidin-5-ylidenemethyl)-benzoic acid
173. [2,4-Dioxo-5-(4-oxo-4*H*-chromen-3-ylmethylene)-thiazolidin-3-yl]-acetic acid
174. [4-(2,4-Dioxo-thiazolidin-5-ylidenemethyl)-phenoxy]-acetic acid
175. 3-(2-Oxo-4-thioxo-thiazolidin-5-ylidenemethyl)-benzoic acid
176. 4-(4-Imino-2-oxo-thiazolidin-5-ylidenemethyl)-phenyl propionate
177. [5-(2-Ethoxycarbonylmethoxy-benzylidene)-2,4-dioxo-thiazolidin-3-yl]-acetic acid
178. 8-(2,4-Dioxo-thiazolidin-5-ylmethyl)-naphthalene-1-carboxylic acid
179. 5-(6-Methyl-4-oxo-4*H*-chromen-3-ylmethylene)-thiazolidine-2,4-dione
180. 2-Acetoxy-5-(2-oxo-4-thioxo-thiazolidin-5-ylidenemethyl)-phenyl acetate
181. 5-(2-Amino-4-oxo-4*H*-chromen-3-ylmethylene)-4-imino-thiazolidin-2-one
182. [5-(6-Ethyl-4-oxo-4*H*-chromen-3-ylmethylene)-2,4-dioxo-thiazolidin-3-yl]-acetic acid

183. 5-(6,8-Dimethyl-4-oxo-4*H*-chromen-3-ylmethyl)-thiazolidine-2,4-dione
184. 5-(6-Isopropyl-4-oxo-4*H*-chromen-3-ylmethylene)-thiazolidine-2,4-dione
185. Methyl 2-(2-oxo-4-thioxo-thiazolidin-5-ylidenemethyl)-benzoate
186. Methyl 3-(4-imino-2-oxo-thiazolidin-5-ylidenemethyl)-1*H*-indole-6-carboxylate
187. [2,4-Dioxo-5-(1-phenyl-ethylidene)-thiazolidin-3-yl]-acetic acid
188. 5-(1-*p*-Tolyl-ethyl)-thiazolidine-2,4-dione
189. 5-[1-(4-Methoxy-phenyl)-ethylidene]-thiazolidine-2,4-dione
190. 5-[1-(3,4-Dichloro-phenyl)-ethylidene]-4-thioxo-thiazolidin-2-one
191. 4-Imino-5-(1-thiophen-2-yl-ethylidene)-thiazolidin-2-one
192. 5-(4-Ethoxy-3-methoxy-benzylidene)-2-imino-thiazolidin-4-one
193. 5-(4-Decyloxy-benzylidene)-2-imino-thiazolidin-4-one
194. 5-(4-Amino-benzylidene)-2-imino-thiazolidin-4-one
195. 2-Imino-5-(4-octyl-benzylidene)-thiazolidin-4-one
196. 5-(2,2-Dimethyl-chroman-6-ylmethylene)-2-imino-thiazolidin-4-one
197. 5-(2,3-Dihydro-benzofuran-5-ylmethylene)-2-imino-thiazolidin-4-one
198. 5-(3,5-Dimethyl-benzylidene)-2-imino-thiazolidin-4-one
199. 5-(4-Diphenylamino-benzylidene)-2-imino-thiazolidin-4-one
200. 5-[4-(2-Hydroxy-ethoxy)-benzylidene]-2-imino-thiazolidin-4-one
201. 2-Imino-5-(4-methanesulphonyl-benzylidene)-thiazolidin-4-one
202. 2-Imino-5-(3-naphthalen-2-yl-allylidene)-thiazolidin-4-one
203. 5-[3,7-Dimethyl-9-(2,6,6-trimethyl-cyclohex-1-enyl)-nona-2,4,6,8-tetraenylidene]-2-imino-thiazolidin-4-one
204. 5-(2-Hydroxy-4,6-dimethoxy-benzylidene)-2-imino-thiazolidin-4-one
205. 5-(2,5-Bis-benzyloxy-benzylidene)-2-imino-thiazolidin-4-one
206. 5-[3-(3,4-Diethoxy-2,5-dimethyl-phenyl)-allylidene]-2-imino-thiazolidin-4-one
207. 4-(2-Imino-4-oxo-thiazolidin-5-ylidenemethyl)-benzoic aid
208. 4-(2-Imino-4-oxo-thiazolidin-5-ylidenemethyl)-phenyl propionate
209. 5-(2-Amino-4-oxo-4*H*-chromen-3-ylmethylene)-2-imino-thiazolidin-4-one
210. Methyl 3-(2-imino-4-oxo-thiazolidin-5-ylidenemethyl)-1*H*-indole-6-carboxylate
211. 2-Imino-5-(1-thiophen-2-yl-ethylidene)-thiazolidin-4-one
212. {5-[1-(3,5-Dihydroxy-phenyl)-ethylidene]-2,4-dioxo-thiazolidin-3-yl}-acetic acid
213. 5-(2,4-Bis-benzyloxy-benzyl)-thiazolidine-2,4-dione
214. 5-Pyridin-2-ylmethyl-thiazolidine-2,4-dione
215. 5-(4-Benzyloxy-3,5-dimethoxy-benzyl)-thiazolidine-2,4-dione
216. 5-(2,4-Dioxo-thiazolidin-5-ylmethyl)-2-hydroxy-benzoic acid

217. [4-(2,4-Dioxo-thiazolidin-5-ylmethyl)-phenoxy]-acetic acid
218. 5-[3-(2,4-Dimethoxy-3-methyl-phenyl)-allylidene]-thiazolidine-2,4-dione
219. 5-[3-(2-Hexyloxy-phenyl)-allylidene]-thiazolidine-2,4-dione
220. 5-(3-Benzofuran-2-yl-allylidene)-thiazolidine-2,4-dione
221. 5-[3-(3,4-Dihydroxy-5-methoxy-phenyl)-allylidene]-thiazolidine-2,4-dione
222. 5-(3-Benzo[1,3]dioxol-4-yl-allylidene)-thiazolidine-2,4-dione
223. 5-[3-(4-*tert*-Butoxy-phenyl)-allylidene]-thiazolidine-2,4-dione
224. 5-[3-(3-Amino-phenyl)-allylidene]-thiazolidine-2,4-dione 5-(5-Furan-2-yl-4-methyl-penta-2,4-dienylidene)-thiazolidine-2,4-dione
225. 5-[5-(4-Hydroxy-3-methoxy-phenyl)-penta-2,4-dienylidene]-thiazolidine-2,4-dione
226. 5-[5-(4-*tert*-Butyl-phenyl)-4-methyl-penta-2,4-dienylidene]-thiazolidine-2,4-dione
227. 5-{3-[3-(2-Hydroxy-ethoxy)-phenyl]-allylidene}-thiazolidine-2,4-dione
228. 5-[5-(4-Hydroxy-3,5-dimethoxy-phenyl)-penta-2,4-dienylidene]-thiazolidine-2,4-dione
229. 5-(5-Benzo[*b*]thiophen-2-yl-penta-2,4-dienylidene)-thiazolidine-2,4-dione
230. 5-[3-(2,4-Bis-benzyloxy-phenyl)-allylidene]-thiazolidine-2,4-dione
231. 5-(3-Pyridin-2-yl-allylidene)-thiazolidine-2,4-dione
232. 5-[3-(4-Benzyloxy-3,5-dimethoxy-phenyl)-allylidene]-thiazolidine-2,4-dione
233. 5-(5-Biphenyl-4-yl-penta-2,4-dienylidene)-thiazolidine-2,4-dione
234. 5-[3-(2,4-Dioxo-thiazolidin-5-ylidene)-propenyl]-2-hydroxy-benzoic aid
235. 3-[3-(2,4-Dioxo-thiazolidin-5-ylidene)-propenyl]-benzoic aid
236. 2-Acetoxy-5-[3-(2,4-dioxo-thiazolidin-5-ylidene)-propenyl]-phenyl acetate
237. Methyl 2-[3-(2,4-dioxo-thiazolidin-5-ylidene)-propenyl]-benzoate
238. 5-[3-(3,4-Dichloro-phenyl)-but-2-enylidene]-thiazolidine-2,4-dione

The following Examples show some process variants which can be used for the synthesis of the compounds in accordance with the invention. However, they are not intended to be a limitation of the object of the invention. The structure of the compounds was proven by ^{1}H- and, where necessary, by ^{13}C-NMR spectroscopy. The purity of the substances was determined by C, H, N, P analysis as well as by thin-layer chromatography.

Example 1

General Process A:

A solution of 5.4 mmol of aldehyde of the formula R-CHO, wherein R has the significance given above, and 5.4 mmol of thiazolidine-2,4-dione in 30 ml of abs. toluene is treated with catalytic amounts of piperidinium acetate and heated at reflux for 5 to 10 hours. Thereafter, the mixture is cooled to 0°C. The precipitate is filtered off under suction, rinsed with diethyl ether and dried.

5-Benzylidene-thiazolidine-2,4-dione (1)
Colourless crystals; m.p. 241-3°C

5-(2-Hydroxy-benzylidene)-thiazolidine-2,4-dione (2)
Dark yellow crystals; m.p. 249-51°C

5-(4-Methoxy-benzylidene)-thiazolidine-2,4-dione (3)
Pale yellow crystals; m.p. 213-5°C

5-(3,4-Dimethoxy-benzylidene)-thiazolidine-2,4-dione (4)
Yellow crystals; 215-7°C

5-Benzo[1,3]dioxol-5-ylmethylene-thiazolidine-2,4-dione (5)
Yellow crystals; 248-9°C

5-(4-Isopropyl-benzylidene)-thiazolidine-2,4-dione (6)
Colourless crystals; m.p. 149-51°C

5-(4-Dimethylamino-benzylidene)-thiazolidine-2,4-dione (7)
Red-brown crystals; m.p. >280°C

5-Naphthalen-2-ylmethylene-thiazolidine-2,4-dione (8)
Yellow crystals; m.p. 196-8°C

5-Phenthylidene-thiazolidine-2,4-dione (9)
Colourless crystals; m.p. >280°C

5-[2-(2-Hydroxy-phenyl)-ethylidene]-thiazolidine-2,4-dione (10)
Yellow crystals (sic); m.p. 212-5°C (dec.)

5-[2-(3,4-Dimethoxy-phenyl)-ethylidene]-thiazolidine-2,4-dione (11)
Pale yellow crystals; m.p. 282-5°C (dec.)

5-[2-(4-Isopropyl-phenyl)-ethylidene]-thiazolidine-2,4-dione (12)
Beige crystals; m.p. >280°C

5-[2-(4-Dimethylamino-phenyl)-ethylidene]-thiazolidine-2,4-dione (13)
Orange-yellow crystals; m.p. >280°C

5-Thiophen-2-ylmethylene-thiazolidine-2,4-dione (14)
Yellow crystals; m.p. >280°C

5-Thiophen-3-ylmethylene-thiazolidine-2,4-dione (15)
Beige crystals; m.p. >280°C

5-Naphthalen-1-ylmethylene-thiazolidine-2,4-dione (16)
Pale yellow crystals; m.p. >280°C

5-(1H-Indol-3-ylmethylene)-thiazolidine-2,4-dione (17)
Yellow crystals; m.p. >280°C

5-(4-Benzyloxy-benzylidene)-thiazolidine-2,4-dione (18)
Beige crystals; m.p. 215-8°C

5-Furan-2-ylmethylene-thiazolidine-2,4-dione (19)
Beige crystals; m.p. 228-30°C

5-(4-Propionyl-benzylidene)-thiazolidine-2,4-dione (20)
Pale yellow crystals; m.p. 182-5°C

5-Benzo[b]thiophen-2-ylmethylene-thiazolidine-2,4-dione (21)
Yellow crystals; m.p. >240°C

5-(3-Benzo[b]thiophen-2-yl-allylidene)-thiazolidine-2,4-dione (22)
Yellow crystals; m.p. >240°C

5-(5-Benzo[b]thiophen-2-yl-penta-2,4-dienylidene)-thiazolidine-2,4-dione (23)
Brown crystals; m.p. 210°C (dec.)

5-(3-Phenoxy-benzyl)-thiazolidine-2,4-dione (24)
Beige crystals; m.p. 207°C (dec.)

5-[3-(5,6-Diethoxy-benzo[b]thiophen-2-yl)-allylidene]-thiazolidine-2,4-dione (25)
Orange-red crystals,; m.p. 253-5°C

5-[3-(3,4-Diethoxy-2,5-dimethyl-phenyl)-allylidene]-thiazolidine-2,4-dione (26)
Yellow crystals; m.p. 193-6°C

Example 2
General Process B:

14 mmol of aldehyde of the formula R-CHO, wherein R has the given significance, and 10 mmol of ethyl 2,4-dioxo-thiazolidin-3-ylacetate (Pharmazie 40 727-8 (1985)) are heated under reflux together with 30 mmol of sodium acetate and 40 ml of glacial acetic acid for 6-18 hours. After cooling the mixture is poured into H_2O The precipitate is filtered off under suction, rinsed with H_2O and dried. For purification, it is chromatographed over silica gel with ethyl acetate/heptane.

Ethyl 5-3-(5,6-diethoxy-benzo[b]thiophen-2-yl)-allylidene]-2,4-dioxo-thiazolidin-3-yl-acetate (27)
Orange crystals; m.p. 193-5°C

Ethyl 5-(3,5-di-tert-butyl-4-hydroxy-benzylidene)-2,4-dioxo-thiazolidin-3-yl]-acetate (28)

Yellow crystals; m.p. 138-41°C

Methyl 5-(3,4-Diethoxy-2,5-dimethyl-benzylidene)-2,4-dioxo-thiazolidin-3-yl]-acetate (29)

Yellow crystals; m.p. 70-5°C

Methyl 5-(3,4-Dihydroxy-2,5-dimethyl-benzylidene)-2,4-dioxo-thiazolidin-3-yl]-acetate (30)

Ochre-coloured crystals; m.p. 220-3°C

Methyl 5-[3-(5,6-Diethoxy-benzo[b]thiophen-2-yl)-allylidene]-2,4-dioxo-thiazolidin-3-yl-acetate (31)

Ochre coloured crystals; m.p. 160-4°C

Example 3

General Process C:

7 mmol of the corresponding ethyl acetate derivative are then treated with 0.4 ml of sulphuric acid and 18 ml of formic acid. The formic acid is removed in a vacuum and the residue is recrystallized from water/acetonitrile.

[5-(3,5-Di-tert-butyl-4-hydroxy-benzylidene)-2,4-dioxo-thiazolidin-3-yl]-acetic acid (32)

Pale yellow crystals; m.p. 130-5°C

[5-(3,4-Diethoxy-2,5-dimethyl-benzylidene)-2,4-dioxo-thiazolidin-3-yl]-acetic acid (33)

Colourless crystals; m.p. 180-3°C

[5-(3,4-Dihydroxy-2,5-dimethyl-benzylidene)-2,4-dioxo-thiazolidin-3-yl]-acetic acid (34)

Yellow crystals; m.p. 230°C (dec.)

5-[3-(5,6-Diethoxy-benzo[b]thiophen-2-yl)-allylidene]-2,4-dioxo-thiazolidin-3-yl-acetic acid (35)
Orange crystals; m.p. 235°C (dec.)

5-[3-Methyl-5-(2,6,6-trimethyl-cyclohex-1-enyl)-penta-2,4-dienylidene]-2,4-dioxo-thiazolidin-3-yl-acetic acid (36)
Orange crystals; m.p. 135°C (dec.)

5-[3-(3,4-Diethoxy-2,5-dimethyl-phenyl)-allylidene]-2,4-dioxo-thiazolidin-3-yl-acetic acid (37)
Yellow crystals; m.p. 190-3°C

[5-(3-Biphenyl-4-yl-allylidene)-2,4-dioxo-thiazolidin-3-yl]-acetic acid (38)
Orange crystals; m.p. 215°C (dec.)

Example 4
General Process D:

a. 10 mmol of 4-thioxo-thiazolidin-2-one (Chem. Heterocycl. Compds. EN 3 533-4 (1967) and 10 mmol of aldehyde R-CHO, wherein R has the given significance, are taken up in 10 ml of glacial acetic acid, treated with 1 g of sodium acetate and heated at reflux for 10-60 min. After cooling 10 ml of H_2O are added thereto, the precipitate is filtered off and rinsed with H_2O and dried. For purification, it is recrystallized from (sic) methanol.

b. 10 mmol of the corresponding 5-alkyl-4-thioxo-thiazolidin-2-one derivative are treated with 3.25 mmol of P_2S_5 in 10 ml of abs. dioxan for 3 to 10 hours. Thereafter, active charcoal is added and the mixture is heated for a further 30 min. The mixture is filtered and the solvent is removed under a vacuum. The residue is recrystallized from water.

Example 5

General Process E:

a. 10 mmol of 4-iminothiazolidin-2-one one (Chem. Heterocycl. Compds. EN 4 324-5 (1968)) and 10 mmol of aldehyde R-CHO, wherein R has the given significance, are treated with 1 g of sodium acetate and 10 ml of glacial acetic acid. The mixture is heated at reflux for 10 to 60 min., cooled and poured into 60 ml of water. The precipitate is filtered off under suction, rinsed with water and methanol and dried.

b. 10 mmol of the corresponding 5-alkylidene-4-thioxo-thiazolidin-2-one derivative are heated to 100°C with 6 ml of conc. Ammonia for 10 to 60 min. After cooling the precipitate is filtered off under suction and rinsed with water and methanol. For purification, it is crystallized from dioxan.

Example 6

General process F:

10 mmol of the corresponding 5-alkylidene-2,4-thiazolidinedione derivative are hydrogenated in tetrahydrofuran with 1 g of Pd/C 10% at 50 PSI. The catalyst is filtered off and the solvent is removed in a vacuum.. The residue is purified by chromatography over silica gel (heptane/ethyl acetate).

Example 7

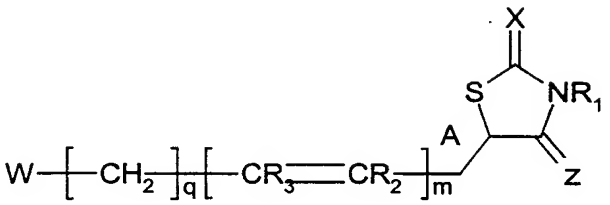
Compounds of general formula (I) were investigated in a suitable assay for the capability of stimulating cyclic adenylate cyclase.

Table I:

Example No.	Name	% cAMP (test conc. 50μM)
22	5-(3-Benzo[b]thiophen-2-yl-allylidene)-thiazolidine-2,4-dione	15
23	5-(5-Benzo[b]thiophen-2-yl-penta-2,4-dienylidene)-thiazolidine-2,4-dione	30
32	[5-(3,5-Di-tert-butyl-4-hydroxy-benzylidene)-2,4-dioxo-thiazolidin-3-yl]-acetic acid	15
36	5-[3-Methyl-5-(2,6,6-trimethyl-cyclohex-1-enyl)-penta-2,4-dienylidene]-2,4-dioxo-thiazolidin-3-yl-acetic acid	20

Patent Claims

1. Use of Compounds of general formula (I)



(I)

in which

m signifies a number between 0-8,

q signifies a number between 0-8

A signifies a single or double bond

R_1 signifies hydrogen or, when X and Z are oxygen, also $-CH_2)-COR_4$ with a = 0-6

R_2,R_3 signify hydrogen or lower alkyl,

whereby R_2 and R_3 can be the same or different and, when m signifies 2-8, R_2 and R_3 in the group $CR_2=CR_3$ can have various significances within the following sequence

R_4 signifies hydroxyl, lower alkoxy or the NR_1R_2 residue, whereby R_1 and R_2 can be the same or different

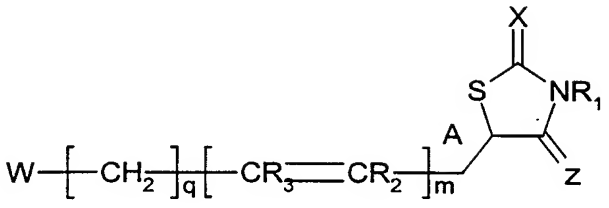
X signifies oxygen or imino

Z signifies oxygen, sulphur or imino

W signifies an optionally mono- or polysubstituted saturated or unsaturated mono-, bi- or tricycle which can contain one or more hetero atoms,

for the preparation of medicaments for the treatment and prevention of metabolic bone disorders,

2. Compounds of general formula (I)



(I)

in which

m signifies a number between 0-8,

q signifies a number between 0-8

A signifies a single or double bond

R_1 signifies hydrogen or, when X and Z are oxygen, also -CH_2)-COR_4 with a = 0-6

R_2,R_3 signify hydrogen or lower alkyl, whereby R_2 and R_3 can be the same or different and, when m signifies 2-8, R_2 and R_3 in the group CR_2=CR_3 can have various significances within the following sequence

R_4 signifies hydroxyl, lower alkoxy or the NR_1R_2 residue, whereby R_1 and R_2 can be the same or different

X signifies oxygen or imino

Z signifies oxygen, sulphur or imino

W signifies an optionally mono- or polysubstituted saturated or unsaturated mono-, bi- or tricycle which can contain one or more hetero atoms,

whereas W is not phenyl, naphthyl, indolyl, benzofuranyl and benzothiophen-yl, if X signifies oxygen, m and q are both 0 and R_1 is hydrogen,

whereas W is not an aminosubstituted phenyl and indolyl, if X signifies imino, m and q both are 0 and R_1 is hydrogen,

as well as their physiologically compatible salts, esters, optically active forms, racemates, tautomers, as well as derivatives which can be metabolized *in vivo* to compounds of general formula (I).

3. Medicament containing at least one compound of general formula (I) according to claim 2 in admixture with usual pharmaceutical adjuvents and carrier material

INTERNATIONAL SEARCH REPORT

Intern ıal Application No
PCT/EP 99/07252

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D277/34 C07D417/06 A61K31/425 C07D277/36 C07D277/40

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	G.STEFANOVIC ET AL: "The synthesis of alpha-methyl-beta-phenylisocysteine and the preparation of substituted thiazolidine-5-carboxylic acids" TETRAHEDRON., vol. 18, 1962, pages 413-418, XP002093194 OXFORD GB * page 414,compound II,page 416* --- -/--	2

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
6 January 2000	14/01/2000

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Henry, J

2

Form PCT/ISA/210 (second sheet) (July 1992)

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
X	CHEMICAL ABSTRACTS, vol. 76, no. 25, 19 June 1972 (1972-06-19) Columbus, Ohio, US; abstract no. 153658q, A.I. GINAK ET AL: "Synthesis of 2,4-thiazolidinediones" page 459; XP002093196 abstract & ZH. PRIKL. KHIM., vol. 45, no. 2, 1972, pages 460-462, leningrad	2
X	CHIEN-PEN LO ET AL: "5-aralkylidene-3-isobutyl-2,4-thiazolidin ediones" JOURNAL OF THE AMERICAN CHEMICAL SOCIETY., vol. 75, 5 October 1953 (1953-10-05), pages 4845-4846, XP002093195 DC US the whole document	2
X	CHEMICAL ABSTRACTS, vol. 61, no. 13, 21 December 1964 (1964-12-21) Columbus, Ohio, US; abstract no. 16059e, LEOPOLD MUSIAL ET AL: "Synthesis of 5-substituted 2,4-thiazolidinedione derivatives with fungicidal activity" XP002093197 abstract & ROCZNIKI CHEM., vol. 38, no. 7, 1964, pages 1105-110,	2
X	CHEMICAL ABSTRACTS, vol. 116, no. 13, 30 March 1992 (1992-03-30) Columbus, Ohio, US; abstract no. 128752c, K. POPOV-PERGAL ET AL: "Condensation of 2,4-dioxotetrahydro-1,3-thiazole with aromatic aldehydes" page 874; XP002093198 abstract & ZH. OBSHCH. KHIM., vol. 61, no. 9, 1991, pages 2112-2116,	2

-/--

2

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
X	CHEMICAL ABSTRACTS, vol. 55, no. 18, 4 September 1961 (1961-09-04) Columbus, Ohio, US; abstract no. 17623c, V.G. ZUBENKO: "Synthesis of 5-arylidene derivatives of 2,4-thiazolidinedione" XP002093199 abstract & TRUDY L'VOV MED INST., vol. 12, 1957, pages 80-82, ---	2
X	CHEMICAL ABSTRACTS, vol. 128, no. 24, 15 June 1998 (1998-06-15) Columbus, Ohio, US; abstract no. 294780c, page 627; XP002093200 abstract & JP 10 101659 A (NITTO CHEMICAL INDUSTRY CO.LTD) 21 April 1998 (1998-04-21) ---	2
X	CHEMICAL ABSTRACTS, vol. 109, no. 9, 29 August 1988 (1988-08-29) Columbus, Ohio, US; abstract no. 73374d, NGUYENKHANG ET AL: "Derivatives of thiazolidinedione having pharmaceutical properties: thizolidine-2,4-dione and its derivatives" page 687; XP002093201 abstract & REV. PHARM.,1986, pages 110-118, ---	1,2
X	EP 0 783 888 A (SANKYO COMPANY LIMITED) 16 July 1997 (1997-07-16) cited in the application claims ---	1-3
X	WO 98 01445 A (SMITHKLINE BEECHAM S.P.A.) 15 January 1998 (1998-01-15) claims ---	1-3
X	US 5 143 929 A (BELLIOTTI THOMAS R ET AL) 1 September 1992 (1992-09-01) the whole document ---	1,2
X	EP 0 559 571 A (ADIR ET COMPAGNIE) 8 September 1993 (1993-09-08) claims ---	1,2
X	EP 0 528 734 A (ADIR ET COMPAGNIE) 24 February 1993 (1993-02-24) claims --- -/--	1,2

2

INTERNATIONAL SEARCH REPORT

Inter nal Application No
PCT/EP 99/07252

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
X	EP 0 434 394 A (ELI LILLY AND COMPANY) 26 June 1991 (1991-06-26) claims	1,2
X	EP 0 398 179 A (NISSHIN FLOUR MILLING CO) 22 November 1990 (1990-11-22) claims	1,2
X	EP 0 316 790 A (NISSHIN FLOUR MILLING CO) 24 May 1989 (1989-05-24) the whole document	1,2
X	EP 0 299 620 A (BEECHAM GROUP PLC) 18 January 1989 (1989-01-18) claims	1,2
X	EP 0 237 138 A (YAMANOUCHI PHARMACEUTICAL CO. LTD) 16 September 1987 (1987-09-16) claims	1,2
X	WO 96 26207 A (NISSAN CHEMICAL IND LTD) 29 August 1996 (1996-08-29) claims	1,2
A	EP 0 691 129 A (ELI LILLY) 10 January 1996 (1996-01-10) claims	1-3

2

Form PCT/ISA/210 (continuation of second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/EP 99/07252

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☒ Claims Nos.: partially 2
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
see FURTHER INFORMATION sheet PCT/ISA/210

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Claims Nos.: partially 2

The initial phase of the search revealed a very large number of documents relevant to the issue of novelty. So many documents were retrieved that it is impossible to determine which parts of the claim 2(compounds per se)may be said to define subject-matter for which protection might legitimately be sought (Article 6 PCT). Consequently, the search report with regard to said claim 2 has been limited to a selection of retrieved novelty-affecting documents with special emphasis to the compounds 1-38 of examples 1-3 and to compounds mentioned pages 9-16 of the description (compounds 1-238)
It should however be noted that the search and the search report can be considered as covering all claimed compounds of the prior art insofar those display an activity for treatment and the prevention of metabolic bone disorders.

INTERNATIONAL SEARCH REPORT

Information on patent family members

Inter ›nal Application No
PCT/EP 99/07252

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
JP 10101659 A	21-04-1998	NONE	
EP 0783888 A	16-07-1997	AU 7650396 A	03-07-1997
		CA 2193751 A	27-06-1997
		CZ 9603827 A	16-07-1997
		HU 9603607 A	28-07-1998
		JP 9235229 A	09-09-1997
		NO 965563 A	27-06-1997
		US 5804590 A	08-09-1998
WO 9801445 A	15-01-1998	EP 0912560 A	06-05-1999
		US 5985905 A	16-11-1999
US 5143929 A	01-09-1992	NONE	
EP 0559571 A	08-09-1993	FR 2688220 A	10-09-1993
		AU 3400893 A	09-09-1993
		CA 2091127 A	07-09-1993
		JP 6009629 A	18-01-1994
		NZ 247068 A	26-01-1994
		ZA 9301593 A	27-09-1993
EP 0528734 A	24-02-1993	FR 2680512 A	26-02-1993
		AT 144503 T	15-11-1996
		AU 645709 B	20-01-1994
		AU 2110892 A	25-02-1993
		CA 2076444 A	21-02-1993
		DE 69214755 D	28-11-1996
		DE 69214755 T	07-05-1997
		DK 528734 T	07-04-1997
		ES 2095432 T	16-02-1997
		GR 3022116 T	31-03-1997
		JP 1998886 C	08-12-1995
		JP 5213913 A	24-08-1993
		JP 7030055 B	05-04-1995
		NZ 244021 A	27-01-1995
		US 5330999 A	19-07-1994
		US 5296605 A	22-03-1994
		US 5266582 A	30-11-1993
		ZA 9206276 A	02-03-1993
EP 0434394 A	26-06-1991	AT 169294 T	15-08-1998
		AU 639734 B	05-08-1993
		AU 6826690 A	27-06-1991
		CA 2032330 A	22-06-1991
		CN 1052668 A,B	03-07-1991
		DE 69032537 D	10-09-1998
		DE 69032537 T	21-01-1999
		ES 2121748 T	16-12-1998
		FI 906273 A	22-06-1991
		HU 216732 B	30-08-1999
		IL 96654 A	29-06-1995
		IL 108962 A	05-12-1996
		JP 4279573 A	05-10-1992
		MX 23803 A	28-02-1994
		NO 300458 B	02-06-1997
		NZ 236472 A	26-03-1993
		PT 96198 A,B	30-09-1991

INTERNATIONAL SEARCH REPORT

...formation on patent family members

Inter... ...nal Application No
PCT/EP 99/07252

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP 0434394 A		RU 2036915 C	09-06-1995
		RU 2050355 C	20-12-1995
		US 5387690 A	07-02-1995
		US 5216002 A	01-06-1993
EP 0398179 A	22-11-1990	DE 69024843 D	29-02-1996
		DE 69024843 T	30-05-1996
		KR 9608245 B	21-06-1996
		US 5116855 A	26-05-1992
		CA 2016665 A	19-11-1990
		JP 3072471 A	27-03-1991
EP 0316790 A	24-05-1989	CA 1336837 A	29-08-1995
		DE 3883164 A	16-09-1993
		DE 3883164 T	02-12-1993
		ES 2059471 T	16-11-1994
		JP 1230565 A	14-09-1989
		JP 2645114 B	25-08-1997
		KR 9609424 B	19-07-1996
		US 4897406 A	30-01-1990
EP 0299620 A	18-01-1989	AU 1767588 A	15-12-1988
		DK 321088 A	14-12-1988
		JP 1013088 A	17-01-1989
		PT 87717 A,B	01-07-1988
EP 0237138 A	16-09-1987	AU 6740187 A	09-07-1987
		DK 4487 A	08-07-1987
		JP 63165368 A	08-07-1988
WO 9626207 A	29-08-1996	AU 4731196 A	11-09-1996
		JP 9235284 A	09-09-1997
		ZA 9601478 A	28-08-1996
EP 691129 A	10-01-1996	US 5476865 A	19-12-1995
		CA 2153213 A	07-01-1996
		JP 8040897 A	13-02-1996